

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

LUCIW, et al.

vs.

CHANG, et al.

Interference No. 103,659

Michael Sofocleous
Administrative Patent Judge

DECLARATION OF JOHN A.T. YOUNG, Ph.D.

BOX INTERFERENCE
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, John A.T. Young, Ph.D., hereby declare:

1. I am an Assistant Professor in the Department of Microbiology and Molecular Genetics at Harvard Medical School. I trained as a graduate student, cloning and sequencing genes that govern immune response functions, at the Imperial Cancer Research Fund and University College, London, from 1983 to 1987. I received a Ph.D. in Human Genetics from University College, London, United Kingdom in 1987. I studied retrovirology as a postdoctoral fellow with Dr. Harold Varmus¹ at the University of California, San Francisco from 1987 to 1992. Other details of my background and qualifications are set forth in my curriculum vitae (attached hereto).

The '339 Application

2. I have been asked to analyze whether a scientist of ordinary skill in October 1984 could have followed the steps set forth in United States Patent Application Serial Number 859,339 ("the '339 Application," Luciw Doc. Exh. 1) to specifically produce recombinant immunoreactive polypeptides from HIV's envelope region for use in an immunoassay. In my opinion, the

¹ Dr. Varmus is a Nobel laureate and now holds the position of director of the National Institute of Health.

numerous flaws and inaccuracies of the '339 Application would have prevented a scientist in 1984 from doing so.

3. A scientist following the instructions of the '339 Application would have been stymied at the outset because the '339 Application does not indicate how to obtain an HIV clone, the starting material needed to begin the steps described in the '339 Application. Nor does the '339 Application identify a particular HIV clone by reference to a deposit or published source.

4. Even if the application had described how to obtain a clone, none of the embodiments described in the '339 Application teaches how to make an immunoreactive envelope polypeptide. All of the embodiments described in the '339 Application require accurate knowledge of the location or sequence of HIV's envelope gene. The '339 Application lacks such information.

5. In fact, the '339 Application actually points a scientist looking for the location of the envelope gene in the *wrong* direction. For example, Figures 1 and 2 of the application show contradictory restriction and gene maps of the HIV genome. (Of course, because of HIV's variability, restriction maps of different isolates vary. As explained in ¶ 3 above, the '339 Application does not indicate how to obtain the BH10 clone for which Chang provided the restriction maps in Figures 1 and 2.) Based on Figure 1, and the text of the '339 Application on pages 3, 6, and 12, an ordinarily skilled scientist would have wrongly assumed that the HIV genome was arranged like those of HTLV-I and HTLV-II, with a pX or "lor" region located between the 3' end of the envelope gene and the 3' long terminal repeat (LTR). In fact, the HIV genome is actually significantly different from those of HTLV-I and HTLV-II, and one of the important differences is that there is not an equivalent pX or lor region located between the 3' end of the envelope gene and the 3'-LTR. Based on Figures 1 and 2, a scientist would have been completely misled about the placement of the envelope gene relative to the restriction enzyme sites in the HIV genome. For example, an EcoRI site that is actually located upstream of the envelope gene is shown in the '339 Application both as contained within the envelope gene (Figure 1) and upstream of the envelope gene (Figure 2). Also, a BglIII site which is actually located in the

envelope gene, is shown in the '339 Application as within a "pX" region which does not exist in the HIV genome (Figure 1). Finally, a HindIII site that is actually located in the envelope gene is shown as being located in the region wrongly presumed to be the "pX" gene (Figures 1 and 2).

6. In addition, a comparison of Figure 3, a nucleotide sequence confusingly mis-described as "encompassing" env, with the later published sequence of the HIV genome (*Ratner* 1985, Luciw Doc. Exh. 1), reveals that Figure 3 consists mostly of DNA sequence upstream of the envelope open reading frame (of the 3,112 nucleotides in Figure 3, only 883 (28%) are from envelope), and contains only about one-third (883 out of 2588 nucleotides or 34%) of the envelope open reading frame.

7. The first embodiment (beginning on page 7) directs that an HIV clone be cut "with restriction enzymes to produce DNA fragments. (Figures 1 and 2)" The embodiment further states that "DNA fragments of approximately 200-500bp [base pairs] are isolated from agarose gel, end repaired with T₄ polymerase and ligated to linker DNA." As Figure 2 makes clear, each of the fragments described in Figure 1 are too large to qualify as 200-500bp fragments, and therefore cannot be used in the first embodiment. There are no directions provided to use a specific combination, or combinations, of restriction enzymes to generate the desired fragments of interest. Indeed, even if an ordinarily skilled scientist had interpreted these instructions to perform every possible combination of restriction enzyme digests with those enzymes listed in Figures 1 and 2, all of the fragments from the envelope gene that would have been produced are larger than 200 to 500 base pairs.

8. An ordinarily skilled scientist, upon realizing that the first embodiment could not work as literally written, would, in my opinion, have abandoned the embodiment altogether as plainly wrong. Even if the scientist had sought additional information in the '339 Application in an attempt to resolve all of the inaccurate information, the embodiment still could not have been read to direct the specific expression of immunoreactive envelope polypeptides. For example, the scientist might have read into the first embodiment a contrary instruction to generate sonicated DNA fragments from an HIV clone (rather than use restriction enzymes), repair with T₄

polymerase, and introduce them into an expression vector. The first embodiment would then require (by implication from the second embodiment) that the bacterial expression vector be introduced into *E. coli*, and cells that had taken up HIV env-containing inserts be identified by a screening procedure using "probes containing the DNA regions of interest," including those specific for the envelope gene. Thus, an essential part of the first embodiment as so altered would be the use of *probes specific to the HIV envelope gene*. However, there is no place in the '339 Application that describes an envelope probe or the actual location of the envelope gene. Instead, the '339 Application offers as the location of the envelope gene a place on the genome which is not, in fact, its correct location. Therefore, no matter how the clones of the first embodiment were generated, a scientist who had attempted to follow its instructions would not have been able specifically to identify an HIV envelope polypeptide.

9. The second embodiment (beginning at the bottom of page 8) directs that the scientist digest "the linearized genomic DNA spanning the *env* gene region with restriction enzymes." The group of purported *env* gene fragments in the '339 Application are "2.3kb KpnI-KpnI fragments; 1.0kb EcoRI-EcoRI fragments and 2.4kb EcoRI-HindIII fragments." The scientist is instructed to randomly shear these fragments, purify the resulting 200-500bp subfragments, and after an end-repair step with *T*₄ polymerase, introduce these fragments into a bacterial expression vector similar to pMR100. These instructions again demonstrate that the authors of the '339 Application were completely unaware of the actual location of the HIV envelope gene, and were working under the assumption that it was located at a wrong position in the HIV genome. Specifically, the 1.0kb EcoRI-EcoRI fragment,² purportedly from *env*, contains none of the envelope gene, but instead contains *sor* and a portion of the *pol* gene. The KpnI-KpnI fragment, also purportedly from *env*, contains a small amount of env DNA, but is largely from the *pol* and *sor* regions. Because it contains only a small amount of the envelope gene, and because of the multiple stop codons before the envelope gene, it would not be possible for a scientist to

² I am informed and believe that the isolate used by Chang was the "IIIB" isolate of HIV and that the restriction sites in the '339 Application are from that isolate.

express an envelope polypeptide from a 200-500bp sub-fragment of the KpnI-KpnI fragment using a fusion protein system described in the second embodiment. Although most of the 2.4kb EcoRI-HindIII fragment comes from *env*, it also contains, at its 5' end, some non-envelope DNA. Moreover, the non-envelope portion of the 2.4kb EcoRI-HindIII fragment includes sequences from the Tat, Rev, and Vpu genes, all of which are immunoreactive HIV proteins. If a scientist had generated an immunoreactive polypeptide from random sub-fragments of this group of fragments, the scientist would have been mistakenly led by the '339 Application to believe that the polypeptide was from envelope when, in fact, it was quite likely to be non-envelope.

10. In addition, an ordinarily skilled scientist who wanted to generate any of these particular restriction fragments would have been unable to do so. As explained above, the '339 Application failed to describe how to obtain the BH10 clone. Even if the scientist succeeded in using an isolate of the HIV virus to create a different clone of the HIV genome, the scientist could have had no assurance that the new clone would have the same restriction sites as indicated in the '339 Application. This is due to the substantial differences in the DNA sequences of different isolates of HIV. The significance of this variation when evaluating the Chang '339 and '866 Applications is that no two isolates are likely to have an identical pattern of restriction enzyme sites. Thus, the restriction sites that were disclosed in the description or in the figures of the '339 and '866 Applications may well be absent in another HIV isolate. Thus, a scientist of ordinary skill who wanted to isolate a particular restriction fragment mentioned in the '339 Application would have had no sure way of doing so.

11. The second embodiment also states that "DNA sequencing analysis" should be used to analyze the "open reading frame insert of HTLV-III." Because of the problems with the '339 Application, which describes the wrong location for the envelope gene, such a scientist would have had no way of determining whether the DNA from such an insert was in fact from the envelope gene. An additional problem with the random cloning approach described in the '339 Application is that it cannot be repeated by an ordinarily skilled scientist in a reproducible fashion, because each attempt to follow the instructions will yield different "random" fragments.

12. The third embodiment (beginning on page 11) shares all of the problems of the first and second embodiments. The embodiment begins with the statement that "fragments of HTLV-III DNA of approximately 200-500 bps are isolated," without any explanation of the source of these fragments. Even if a scientist could have generated such fragments, the embodiment instructs the use of HIV envelope gene-specific probes to identify fragments derived from the HIV envelope gene. The embodiment also directs the detailed examination of the desired inserted DNA "spanning the [HIV] *env* gene region" by restriction enzyme mapping and DNA sequence analysis. In order to execute any of these experiments, the scientist would have had to know the precise location or sequence of the envelope gene. Not only is this essential information not disclosed in the '339 Application, there are gross inaccuracies in the description of the placement of the envelope gene in the application (as described above) which would have seriously misled a scientist attempting to follow these instructions.

13. The third embodiment suggests two methods of identifying envelope proteins: sequencing of the DNA inserts used to express those proteins, or the use of gene-specific probes to identify DNA inserts from the envelope region. A DNA probe is a radiolabelled piece of single-stranded DNA whose sequence is complementary to the DNA sequence it is designed to identify (the "target"). When the probe is put in contact with the complementary or "matching" target sequence, it binds to the target sequence. The fact that the probe has bound can be identified by its radiolabel. A gene-specific probe for HIV envelope cannot be constructed unless the location of the target envelope gene on the virus is known or the DNA sequence of the envelope has been accurately obtained and analyzed.

14. Figure 4 of the '339 Application is purportedly "an immunoblot showing the position on an SDS polyacrylamide gel of HTLV-III *env*-Beta-galactosidase fusion proteins." '339 Application at 5. Figure 4 bears some resemblance to a standard format for the Western blot technique, but even if it is a Western blot, the results are uninterpretable. In addition, the '339 Application lacks crucial pieces of information that a scientist would need to interpret such a document. For example, there is no information regarding the nature of the clones, the derivation

of the fragments, or the identity of the antiserum which was used to generate the supposed immunoblot. Also, it is normal scientific practice to run molecular weight markers and to describe the character of immunoreactive polypeptides. The supposed immunoreactive bands on Figure 4 are not apparent, however, and are not identified anywhere in the '339 Application. In fact, the results obtained from the clones marked with a "plus" sign or an "x" are no different from the apparent controls (pMR100 and pMR200). It is my opinion that Figure 4 of the '339 Application does not demonstrate that HIV clones are present on the purported immunoblot, that if such clones are present they are from env, or that they are immunoreactive.

The '866 Application

15. I have also been asked to analyze whether a scientist of ordinary skill in October 1984 could have followed the steps set out in the continuation-in-part application, United States Patent Number 693,866 ("the '866 Application," Luciw Doc. Exh. 2), to produce a recombinant immunoreactive HIV envelope polypeptide for use in an immunoassay. In my opinion, the '866 Application, like the '339 Application, fails to describe how to specifically make an immunoreactive HIV envelope polypeptide.

16. The '866 Application shares many of the problems previously described for the '339 Application. For example, the '866 Application fails to describe how to obtain an HIV clone, the starting material needed to begin all of the steps described in the '866 Application.

17. Like the '339 Application, all of the purported methods in the '866 Application for making an envelope polypeptide require accurate knowledge of the location or sequence of the envelope gene. The '866 Application, however, fails to identify accurately the parameters of the envelope gene. Instead, again based on the wrong assumption that there would be some region similar to pX (lor) of the HTLV-I or HTLV-II, between the envelope gene and the 3' long-terminal repeat of HIV, the application describes a region of the HIV genome with a single open reading frame designated *env-lor*, that supposedly encodes both Env and Lor products. This description of the open reading frame, which we now know to be that of the actual envelope gene, would have completely confused and misled a scientist working with the instructions of the '866 Application in

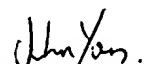
an attempt to produce an envelope polypeptide. First, without knowing where within the “env-lor” open reading frame the env gene and the putative “lor” gene were located, an ordinarily skilled scientist would not have known whether a particular DNA fragment encoded just for *env*, just for *lor*, or for both *env* and *lor*. Indeed, the actual envelope gene is misidentified as “LOR” in Figure 2, and as “ENV-LOR” in Figure 3 of the ‘866 Application. Figure 1 of the ‘866 Application, unchanged from the ‘339 Application, similarly misidentifies the location and relative size of *env*. Thus, following the instructions of the ‘866 Application, a scientist of ordinary skill would not have been able to determine whether a polypeptide expressed from the HIV genome was, in fact, an envelope polypeptide.

18. Furthermore, a scientist working the ‘866 Application would have been confused by the contradictory statements regarding the actual parameters of the HIV envelope gene. For example, the ‘866 Application contains the incorrect statements that the HTLV-III genome “contains a region designated *Px*, located between the *env* gene and the 3’ LTR” and “lor, located between the *env* gene and the 3’ end of the HTLV-III genome.” These two statements—indicating that there are two separate open reading frames for the *env* and putative *lor* DNA sequences—directly contradict another statement in the ‘866 Application that “[b]oth the env DNA sequences and the lor DNA sequences are located within the same open reading frame.” Reading these statements would have further prevented a scientist in 1984 from using the ‘866 Application to generate an immunoreactive HIV envelope polypeptide.

19. Indeed, Chang herself appears to have been confused about the identity of the clones she believed were immunoreactive. According to Figure 2 of the ‘866 Application, clones 127, 121, and 113 are the only purportedly positive clones from the “LOR” region, while clone 76, also from the LOR region, was not immunoreactive. Figure 2 also indicates that the three positive clones come from within the BglII-HindIII portion of the genome. Yet Figure 1 shows that the BglII-HindIII fragment lies completely within the “Px” region of the genome. Based on Figures 1 and 2 of the ‘866 Application, an ordinarily skilled scientist would conclude that Chang believed her only positive came not from envelope, but from “Px.”

20. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: February 19, 1996


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PERSONAL

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Birthdate: February 28, 1961
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ACADEMIC APPOINTMENTS

- 1992 to 1995 Assistant Professor
Department of Microbiology and Immunology
University of California, San Francisco
San Francisco, California
- 1992 to 1995 Assistant Investigator
Gladstone Institute of Virology and Immunology
San Francisco General Hospital
San Francisco, California
- 1992 to 1995 Member, Program in Biological Sciences (PIBS)
Cell Biology Program
University of California, San Francisco
- 1992 to 1995 Member, Biomedical Sciences Program
University of California, San Francisco
- 1995 to Member, Biological and Biomedical Sciences Program,
Harvard Medical School
- 1995 to Member, Committee on Virology, Harvard Medical School

POSTDOCTORAL TRAINING

- 1987-1989 EMBO Postdoctoral Fellow
Department of Microbiology and Immunology
University of California, San Francisco
Advisor: Harold E. Varmus, M.D.
- 1989-1992 Arthritis Foundation Postdoctoral Fellow
Department of Microbiology and Immunology
University of California, San Francisco
Advisor: Harold E. Varmus, M.D.

EDUCATION

- 1983 University of Dundee
Dundee, United Kingdom
B.Sc., Biochemistry (First Class Honours)
- 1987 Imperial Cancer Research Fund and University College
London, United Kingdom
Ph.D., Human Genetics
Thesis: Expression and Polymorphism of HLA-D Region Genes
Ph.D. Advisor: John Trowsdale, Ph.D.

TEACHING EXPERIENCE

- 1992 Co-organizer
Introduction to Cell Biology course
Medicine 412, UCSF
- Discussion Leader
Cell Biology Course 212, UCSF
- 1993 Lecturer
The Biology of AIDS
Biomedical Sciences Minisymposium, UCSF
- 1993 Discussion Leader
Tissue Organization and Morphogenesis course
Biomedical Sciences 210, UCSF
- Discussion Leader
Molecular Biology of Animal Viruses course
Microbiology 208, UCSF
- 1994 Lecturer, The Biology of Virus Infection course
Microbiology 208, UCSF

COMMITTEES

- 1992 to 1995 Member, Dean's Advisory Committee to the UCSF AIDS Clinical Research Center
- 1993 to 1995 Member, Executive Committee of the UCSF Biomedical Sciences Program
- 1993 to 1995 Member, UCSF Student Research Committee

TRAINEES

- 1992 to 1995 Kurt Zingler
Ph.D. Thesis Student
Immunology Program, UCSF
- Jürgen Brojatsch, Ph.D.
Postdoctoral Fellow
- Carole Bélanger, Ph.D.
Postdoctoral Fellow
Fonds de la Recherche en Santé du Québec
- 1993 to 1995 Lynn Connolly
M.D., Ph.D. Thesis Student
Medical Scientist Training Program, UCSF
- Morgan Jenkins, M.D.
Clinical Research Fellow
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INVITED PRESENTATIONS

Invited Chair, Roundtable Discussion on Gene Therapies for AIDS, Second Annual NIH National AIDS Cooperative Drug Discovery and Development Meeting. California, 1988.

Invited Speaker, Banbury Conference on Receptor Mediated Virus Entry into Cells, Cold Spring Harbor Laboratory, 1991.

Invited Speaker, Keystone Symposium on Molecular Biology of Human Pathogenic Viruses. California, 1993.

Invited Speaker, Fifth Workshop on Pathogenesis by Non-acute Retroviruses. France, 1993.

Invited Speaker, Workshop on Immunology and Developmental Biology of the Chicken. Basel Institute of Immunology, Switzerland, 1994.

Invited Speaker, Sixth Workshop on Pathogenesis of Animal Retroviruses. Philadelphia 1994

Invited Speaker, Seventh Workshop on Pathogenesis of Animal Retroviruses. Seattle 1995.

Invited Speaker, FASEB Summer Conference on Principles in Viral, Bacterial, Fungal and Protozoan Pathogenesis. Colorado 1996

Invited Speaker, FASEB Summer Conference on Virus Assembly, Vermont 1996

OTHER PRESENTATIONS

An attempt to specifically alter retroviral tropism using EGF-envelope chimeras. J.A.T. Young, P. Bates, H. Varmus. Poster presentation at Cold Spring Harbor RNA Tumor Viruses meeting. May 1988.

Transfer of susceptibility to ALSV infection into mammalian cells with chicken DNA. P. Bates, J.A.T. Young, and H.E. Varmus. Talk at Cold Spring Harbor RNA Tumor Viruses meeting. May 1989.

The human CD4 protein is efficiently incorporated into ALV particles. J.A.T. Young, P. Bates, K. Willert, and H.E. Varmus. Talk at Cold Spring Harbor RNA Tumor Viruses meeting. May 1990.

An LDL receptor-related protein is the subgroup A ALV receptor. P. Bates, J.A.T. Young, H.E. Varmus. Talk at Cold Spring Harbor RNA Tumor Viruses meeting. May 1992.

Functional characterization of the subgroup A-Avian Leukosis Virus (ALV) receptor gene: Low levels of receptor expression are limiting for virus infection. J.A.T. Young, P. Bates, H.E. Varmus. Talk at Cold Spring Harbor RNA Tumor Viruses meeting. May 1992.

Mutational analysis of the cellular receptor for subgroup A-ALSV. K. Zingler, C. Bélanger, J.A.T. Young. Talk at Cold Spring Harbor Retroviruses meeting. May 1994.

A soluble version of the subgroup A-ALSV receptor blocks infection and binds directly to ALSV-A. L. Connolly, K. Zingler, J.A.T. Young. Talk at Cold Spring Harbor Retroviruses meeting. May 1994

An assay system to determine the relative levels of intermediate and complete DNA forms of HIV-1 DNA following infection. M. Jenkins, J. Naughton, J.A.T. Young. Poster presentation at Cold Spring Harbor Retroviruses meeting. May 1994.

GRANTS

Characterization of ALSV-A Env/Receptor Interactions
NIH: 1R29CAAI62000-01A1
\$615,301, July 1994 to June 1999

An Attempt to Target Retrovirus Vectors to Cells Expression HIV-1 Envelope Proteins
AIDS Clinical Research Center, UCSF
One-year grant (\$25,000). Funded January 26, 1994

Milton Fund (\$12,000) Harvard Medical School, July 1995

Characterizing the Mechanisms of ALSV Entry into Cells
NIH: 1RO1CA70810-01
Submitted June 1, 1995. Decision Pending.

PUBLICATIONS

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2. Young, J.A.T. and Trowsdale, J. (1985) A processed pseudogene in an intron of the HLA-DP β 1 chain gene is a member of the ribosomal protein L32 gene family. *Nucl. Acids Res.* **13**: 8883-8891.
3. Trowsdale, J., Austin, P., Carson, S., Kelly, A., Lamb, J., and Young, J.A.T. (1985) Cloned HLA-D genes: Characterisation and approaches to expression and analysis of function. In: *Human T-cell Clones* (M. Feldmann, J.R. Lamb, and J.N. Woody, eds.), The Human Press, pp 49-57.
4. Bodmer, W.F., Trowsdale, J., Young, J., and Bodmer, J. (1986) Gene clusters and the evolution of the major histocompatibility complex. *Phil. Trans. R. Soc. Lond.* **312**: 303-315.
5. Young, J.A.T., Wilkinson, D., Bodmer, W.F., and Trowsdale, J. (1987) Sequence and evolution of HLA-DR7- and HLA-DRw53-associated β chains. *Proc. Natl. Acad. Sci. USA* **84**: 4924-4933.
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7. Young, J.A.T., Lindsay, J., Bodmer, J.G., and Trowsdale, J. (1988) Epitope recognition by an HLA-DP α chain-specific monoclonal antibody (DP11.1) is influenced by the association of the DP α chain and its polymorphic DP β chain partner. *Hum. Immunol.* **23**: 37-44.
8. Young, J.A.T. (1988) HIV and HLA similarity. Scientific correspondence. *Nature* **333**: 215.
9. Young, J.A.T. and Trowsdale, J. (1990) The HLA-DNA gene is expressed as a 1.1kb mature mRNA species. *Immunogenetics* **31**: 386-388.
10. Young, J.A.T., Bates, P., Willert, K., and Varmus, H.E. (1990) Efficient incorporation of human CD4 protein into Avian Leukosis Virus particles. *Science* **250**: 1421-1423.
11. Young, J.A.T., Bates, P., and Varmus, H.E. (1993) Isolation of a chicken gene that confers susceptibility to infection by subgroup A avian leukosis and sarcoma viruses. *J. Virol.* **67**: 1811-1816.
12. Bates, P., Young, J.A.T., and Varmus, H.E. (1993) A receptor for subgroup A Rous sarcoma virus is related to the low density lipoprotein receptor. *Cell* **74**: 1043-1051.
13. Connolly, L., Zingler, K., and Young, J.A.T. (1994) A soluble form of a receptor for subgroup A avian leukosis and sarcoma viruses (ALSV-A) blocks infection and binds directly to ALSV-A. *J. Virol.* **68**: 2760-2764.
14. Young, J.A.T., Bates, P.F., and Varmus, H.E. A protein related to the LDL receptor is a cellular receptor specific for subgroup A-avian leukosis and sarcoma viruses. In:

Receptor-mediated Virus Entry into Cells. (E. Wimmer, ed.) Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

15. Young, J.A.T. The replication cycle of HIV-1. In: *The AIDS Knowledge Base.* (Cohen, P., Sande, M., Volberding, P., et al., eds.) Little Brown, New York, NY.
16. Federspiel, M.J., Bates, P., Young, J.A.T., Varmus, H.E., and Hughes, S.H. A system for tissue-specific gene targeting: Transgenic mice susceptible to subgroup A avian leukosis virus-based retroviral vectors. *Proc. Natl. Acad. Sci. USA.* **91:** 11241-11245
17. Bélanger, C., Zingler, K., and Young, J.A.T. Importance of cysteines in the LDLR-related domain of the ALSV-A receptor for viral entry. *J. Virol.* **69:** 1019-1024.
18. Zingler, K., Bélanger, C., Peters, R., Agard, D. and Young, J.A.T. Identification and characterization of the viral interaction determinant of the ALV-A receptor. *J. Virol.* **, 69:** 4261-4266